

Pharmacokinetic interaction studies of atosiban with labetalol or betamethasone in healthy female volunteers

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Objectives In two separate trials, we studied the concomitant administration of atosiban with labetalol and betamethasone to determine any possibility of a clinically relevant pharmacokinetic interaction.

Design Study 1 was an open-label, single dose atosiban, multiple dose labetalol, interaction study. Study 2 was an open-label, randomised, three-period crossover pharmacokinetic study.

Setting The studies were carried out at the Clinical Pharmacology Unit of AAI Deutschland GmbH & Co KG, Neu-Ulm, Germany.

Population The study population consisted of healthy female volunteers.

Methods In Study 1, 14 healthy female volunteers participated. On study day 1, a 12-hour intravenous infusion of 114.75 mg atosiban was administered; on days 2–4, participants received labetalol orally (100 mg twice daily), and on study day 5 they received the combined treatment. In Study 2, a total of 18 healthy female volunteers received, on three separate occasions, a 12-hour intravenous infusion of 114.75 mg atosiban, a single intramuscular injection of 12 mg betamethasone or the two drugs in combination.

Main outcome measure For Study 1, the outcome parameter for atosiban was area under the plasma concentration–time curve (AUC); the study parameters for labetalol were AUC, maximum plasma concentration (C_{\max}) and time to C_{\max} (t_{\max}). In Study 2, AUC, C_{\max} and time to C_{\max} (t_{\max}) were assessed for atosiban and betamethasone.

Results Labetalol had no clinically relevant influence on the bioavailability (AUC) of atosiban. For labetalol, the co-administration with atosiban did not affect the extent of bioavailability, however, C_{\max} decreased by 36% and t_{\max} increased by 45 minutes. The C_{\min} was not affected by atosiban. The betamethasone and atosiban combination led to similar mean plasma concentration–time curves as the administration of each substance alone. Pharmacokinetic parameters (AUC, C_{\max} , t_{\max}) did not differ markedly between treatments and all 90% CIs for ratios between treatments were fully within limits (80–125%). The co-administration of atosiban with labetalol or betamethasone resulted in similar tolerability to each substance alone.

Conclusion The co-administration of atosiban with betamethasone or labetalol had no clinically relevant influence on their bioavailability or tolerability.

INTRODUCTION

Preterm birth is a major cause of neonatal morbidity and mortality.^{1,2} Spontaneous preterm labour potentially leading to preterm delivery may be suppressed by the pharmacological inhibition of uterine activity. Atosiban is a synthetic nonapeptide, which acts as a competitive antagonist of the human oxytocin receptor, and thereby reduces spontaneous preterm uterine activity.^{3–7} Atosiban has recently been approved throughout Europe for the treatment of pregnant women with threatening preterm delivery. The onset of uterus relaxation is rapid following a standard atosiban regimen of a bolus injection of 6.75 mg,

followed by an infusion of 18 mg/h for 3 hours and subsequently 6 mg/h for 9 hours, with uterine contractions being reduced within 10 minutes to achieve a stable uterine quiescence for 12 hours.³

In vitro studies in human liver microsomes have shown that atosiban is a poor substrate for the cytochrome P450 system (unpublished data), indicating that its cytochrome P450-mediated metabolism is of little clinical relevance in humans *in vivo*. In support of this, *in vivo* studies have shown that atosiban is excreted either unchanged through urine and faeces, or by sequential hydrolysis of C-terminal amino acids (unpublished data). No inhibitory effects of 60 μ M atosiban were found on the cytochrome P450 enzymes in human liver microsomes, suggesting that it is unlikely that atosiban will cause clinically significant inhibition of cytochrome P450-mediated activities *in vivo* (unpublished data).

The prevalence of pregnancy-induced hypertension is approximately 10%, and is usually associated with pre-eclampsia.⁸ The combined α - and β -adrenergic receptor antagonist, labetalol, is one of the most frequently prescribed antihypertensives in pregnant women,⁸ mainly due to the

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fact that some antihypertensives, such as diuretics and angiotensin converting enzyme (ACE) inhibitors, are contraindicated during pregnancy due to fetal toxicity or side effects.⁹ Therefore, due to the frequent co-administration of atosiban and labetalol, it is important to assess the risk of a pharmacokinetic interaction between the two drugs.

Labetalol is a pharmacokinetically complex drug, which consists of four diastereomers. It is well absorbed, but undergoes considerable first-pass metabolism, with an oral availability of 20–30%.^{10,11} Approximately 5% of available drug is excreted unchanged in urine, whereas the remaining part is eliminated by oxidative metabolism and glucuronidation in the liver.^{10,11} However, there is limited knowledge about its hepatic metabolism and the identity of the cytochrome P450 enzymes involved in the metabolism is unknown.

At present, it is estimated that the corticosteroids, betamethasone or dexamethasone, are administered in almost all women in preterm labour in order to increase fetal lung maturation.^{12,13} In a clinical setting, atosiban and betamethasone will often be used concomitantly, as the administration of atosiban will delay preterm delivery, thus leaving enough time for betamethasone to be effective. The corticosteroids are either excreted unchanged in urine (approximately 50%) or as glucuronides and sulphates formed by oxidation and conjugation in the liver.^{14,15}

Although current knowledge of the metabolism and elimination of atosiban indicates only a very small risk of drug–drug interactions, two open-label interaction studies in healthy female volunteers were conducted to investigate the pharmacokinetic implications of the co-administration of atosiban with either labetalol or betamethasone.

METHODS

Two open-label studies were carried out at the Clinical Pharmacology Unit of AAI Deutschland, Neu-Ulm, Germany. They were approved by the Ethics Committee in Freiburg, Germany and the Ethics Committee of the Bavarian Chamber of Physicians, Germany and conducted according to ICH Good Clinical Practice¹⁶ and in compliance with the Declaration of Helsinki (last amended at Somerset West in October 1996). Participants were informed of the purpose of the studies and had to give their voluntary signed informed consent before being enrolled.

For both studies, healthy female volunteers, either non-smokers or smokers (<10 cigarettes per day), with adequate contraception were recruited from the local population. All participants were screened within three weeks of the planned first drug administration and had to be healthy according to medical history, complete physical examination, electrocardiogram (ECG), tests for alcohol and drugs and routine laboratory measurements of blood (hepatitis A/B, HIV, pregnancy) and urine. The exclusion criteria included a history of clinical relevant allergy, respiratory tract disorders, drug hypersensitivity, hepatic or renal

disorders, endocrine disorders, hypotension, heart disease, neurological or psychiatric illness and pregnancy. The participants were only included when all pre-study examination procedures had demonstrated compliance to all the inclusion criteria and none of the exclusion criteria.

The first study (Study 1) was an open-label, single-dose atosiban, multiple-dose labetalol, interaction study. Participants were admitted to the Clinical Pharmacology Unit on the evening before the first atosiban infusion and discharged 24 hours after the combined treatment of atosiban administered by infusion and labetalol given orally (study day 5, see below). The atosiban infusion was commenced on study day 1 (Fig. 1).

The second study (Study 2) was an open-label, single-dose, randomised, three-way crossover interaction study. Participants were admitted to the Clinical Pharmacology Unit on the evening before drug administration in each of the three periods. The next morning (study day 1), the investigational drug was given (Fig. 1). Participants were advised to avoid heavy physical exertion during their time of confinement. The washout period between drug administrations was seven days. Participants were discharged 24 hours after the intramuscular injection of betamethasone or start of the infusion of atosiban.

For both studies, atosiban (Tractocile, Ferring, Sweden) was administered as a bolus injection of 6.75 mg, followed by an infusion of 18 mg/h for 3 hours, and subsequently 6 mg/h for 9 hours. A total dose of 114.75 mg in a total volume of 144.9 mL 5% glucose solution was infused over 12 hours.

In Study 1, labetalol (Trandate, GlaxoWellcome, Austria) was administered orally as 100 mg tablets twice daily. On study day 1, the women received the infusion of atosiban (Treatment A). From the morning of day 2 to the evening of day 4 they received labetalol every 12 hours (Treatment B). On day 5, they received combination therapy of the atosiban infusion over 12 hours and labetalol in the morning and evening (Treatment A + B). The start of the atosiban infusion was performed simultaneously with the morning dose of labetalol (Fig. 1). The dosing schemes for atosiban and labetalol are in accordance with clinical practice for the use of the two drugs.

In Study 2, betamethasone (Celestan, Essex Pharma, Germany) was administered by intramuscular injection of 12 mg/3 mL into the gluteus muscle. During two of the three treatment periods, atosiban (Treatment A) or betamethasone (Treatment B) was administered as monotherapy. In the third treatment period, betamethasone and atosiban were combined (Treatment A + B). During this period, betamethasone and the start of the infusion of atosiban were administered simultaneously and at the same dosage as in the monotherapy periods (Fig. 1). The dosing schemes for atosiban and betamethasone are in accordance with clinical practice for the use of the two drugs.

For both studies, a post-study examination (as for screening visit 1, except tests for alcohol, drugs, hepatitis A/B,

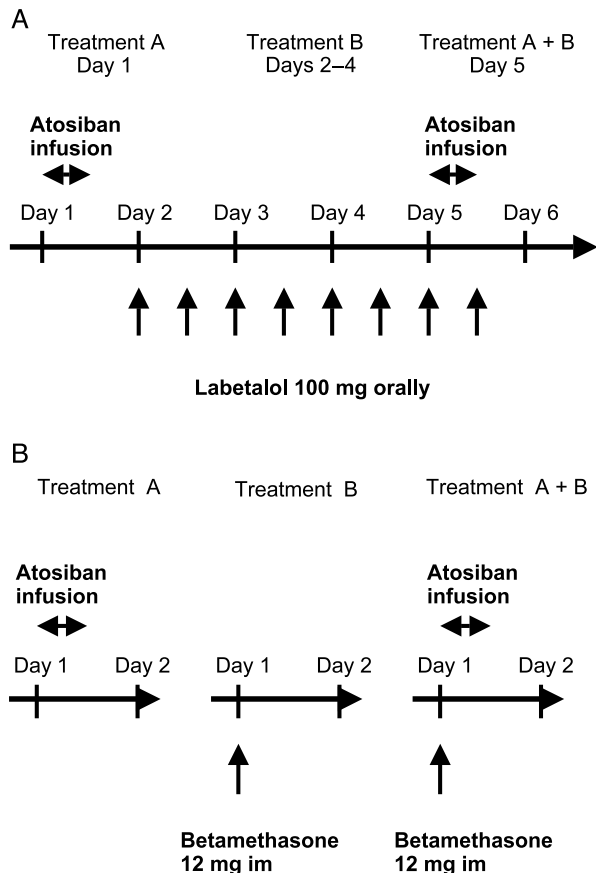


Fig. 1. Dosing schemes for (A) the atosiban–labetalol study (Study 1) and (B) the atosiban–betamethasone study (Study 2). In Study 2, the sequence of the three treatments for each participant was randomised. The atosiban infusion was given as a bolus injection of 6.75 mg, followed by an infusion of 18 mg/h for 3 hours, and subsequently 6 mg/h for 9 hours. Labetalol 100 mg orally was given twice daily. Betamethasone was administered as a single 12 mg intramuscular injection.

HIV and pregnancy) was performed within 14 days of the last drug administration. For safety reasons, blood pressure, heart rate and oral body temperature were measured during the pre-study examination, on day 1 of each study period and at the post-study examination. Adverse events were monitored continuously throughout the study.

For the analysis of atosiban, blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) tubes with decreasing frequencies between 0 hours (pre-infusion) and 18 hours after the start of the infusion. The plasma was separated and stored at -70°C until assayed. All samples were analysed with a validated radio-immunoassay (RIA) at AAI Deutschland, Germany. The intra-assay precision was 5.4% to 14.0% and the intra-assay accuracy was -5.2% to 9.0% . The inter-assay precision was better than 14.0% at all concentrations tested. The inter-assay accuracy was better than 6.2%. The lower limit of quantification was 0.3 ng mL^{-1} .

For the analysis of labetalol, blood samples were drawn into EDTA tubes with relevant intervals between 0 (pre-dose)

and 24 hours after morning administration; the 12-hour sample was drawn immediately prior to the evening dose of labetalol. The plasma was separated and stored at -20°C until analysis. The concentrations of labetalol were analysed by a validated high-performance liquid chromatography (HPLC) with fluorescence detection at AAI Deutschland. The intra-assay precision was 1.3% to 5.9% and the intra-assay accuracy was 1.2% to 2.7%. The inter-assay precision was 1.5% to 6.7%. The inter-assay accuracy was better than 2.2%. The lower limit of quantification was 1 ng mL^{-1} .

For the analysis of betamethasone, blood samples were drawn into 10 mL lithium-heparinised tubes with decreasing frequency between 0 hour (pre-dose) and 48 hours after drug administration. The plasma was separated and stored at -20°C until analysis. The concentrations of betamethasone were analysed by a validated HPLC with ultraviolet (UV) detection at AAI Deutschland. The intra-assay precision was 2.1% to 5.0% and the intra-assay accuracy was -0.3% to 6.4%. The inter-assay precision was 3.2% to 8.2%. The inter-assay accuracy was 0.5% to 2.2%. The lower limit of quantification was 1 ng mL^{-1} .

Pharmacokinetic parameters for both studies were estimated by non-compartmental methods using the SAS software (SAS Inst., version 6, 1990).

For Study 1, the following pharmacokinetic parameters were calculated for atosiban during each treatment: measured maximum concentration (C_{max}) and area under the plasma concentration–time curve from time 0 extrapolated to infinity (AUC).

For labetalol, area under the curve at steady state (AUC_{ss}), C_{max} , measured minimal concentration during steady state (C_{min}) and time to C_{max} (t_{max}) were calculated. Values for C_{max} and t_{max} were calculated for two periods: $C_{\text{max}1}$ and $t_{\text{max}1}$ refer to the values calculated for the oral dose of labetalol given simultaneously with the start of atosiban infusion and $C_{\text{max}2}$ and $t_{\text{max}2}$ refer to the values calculated for the dose of labetalol given 12 hours later. In Study 2, C_{max} , t_{max} and AUC were calculated for each treatment.

For both studies, a lack of an interaction for the pharmacokinetic parameters was tested by applying bioequivalence criteria^{17,18} for C_{max} and AUC by analysis of variance (ANOVA), utilising general linear models (GLM) on in-transformed data (SAS Inst., version 6, 1990). Ratios of the means of the combined *versus* the single treatment were derived together with the corresponding 90% confidence intervals (CIs). According to Steinijans *et al.*,¹⁷ bioequivalence could be stated if the 90% CI of the ratio $\mu_{\text{combined}}/\mu_{\text{single}}$ was fully contained within the acceptance range for AUC and C_{max} . For AUC, a (75%, 133%) acceptance range was used for Study 1 and the customary (80%, 125%) range was used for Study 2, whereas a wider range of (70%, 143%) was accepted for C_{max} , considering that this parameter is intrinsically more variable without leading to any safety or efficacy problems.¹⁸ Observed t_{max} values were evaluated based on the non-parametric Pratt–Wilcoxon test¹⁹ together with the derivation of non-parametric CIs

according to the Tukey test.²⁰ Safety data were only evaluated quantitatively.

In the first study, the sample size calculations were based on previously found values of within-subject coefficients of variation (CV) of 20–23% for the AUC of labetalol.^{21,22} Provided that AUC with and without atosiban co-administration does not differ in the mean by more than 5% and relating to the acceptance range (75%, 133%), it was estimated that at least 14 subjects would be necessary to allow a power >80% for a statistical conclusion of a lack of an interaction. Based on these assumptions and with 14 participants, it allows for a CV for AUC of atosiban of 23%, which is within the range of what could be expected for atosiban from earlier trials.⁴

In Study 2, taking into account the between-subject CV of 20% for betamethasone after intramuscular administration, it was estimated that at least 18 participants would be necessary to allow a power >80% for a statistical conclusion of a lack of an interaction.²³ Based on these assumptions and with 18 participants, it allows for a CV for AUC of atosiban of 19%, which again is within the range expected from previous studies.⁴

RESULTS

Fourteen healthy females aged 18–45 years (mean 30 years) and with a weight of 51 to 75 kg (mean 60 kg) participated in Study 1. In Study 2, 18 healthy females aged 21–45 years (mean 35 years) and with a weight between 51 and 73 kg (mean 60 kg) were enrolled.

In Study 1, one participant requested to be withdrawn from the study on day 2, due to pharyngitis (not drug related). The participant was not replaced, as the loss of statistical power was considered to be acceptable. All

pharmacokinetic parameters were calculated for 13 participants. For three participants, the AUC for atosiban could not be calculated in one of the periods, as the concentration–time profile in the elimination phase did not show a recognisable log-linear decreasing trend. Thus, comparison of AUC for atosiban was based on results from 10 participants only. For Study 2, all 18 participants completed the treatment.

In Study 1, treatment with atosiban alone or in combination with labetalol resulted in similar mean concentration–time curves (Fig. 2). In addition, the co-administration of labetalol had no clinically relevant influence on the bioavailability of atosiban assessed by AUC, and the 90% CIs for the ratio between treatments were well within limits (75%, 133%) (Table 1).

For labetalol, the co-administration of atosiban did not affect bioavailability, in terms of AUC_{ss} (Table 1 and Fig. 3). However, the C_{max} and t_{max} were assessed after both a morning dose (C_{max1} and t_{max1}) and an evening dose (C_{max2} and t_{max2}) of labetalol. For the morning dose, the C_{max1} following simultaneous administration was lowered by 36% (46.5 vs 72.4 ng mL⁻¹) and the t_{max1} was increased by 45 minutes (Table 1). In contrast, the evening dose of labetalol was given immediately after the infusion of atosiban was stopped, and in this case, the combination of labetalol and atosiban did not influence the C_{max2} and t_{max2} for labetalol. In addition, the overall C_{min} of labetalol observed during the 24-hour steady-state interval was not affected by atosiban (Table 1).

In the second study, treatment with atosiban alone or in combination with an intramuscular dose of betamethasone led to similar mean concentration–time curves (Fig. 4). Mean concentration–time curves of betamethasone were also similar, independent of whether atosiban was co-administered or not (Fig. 5). AUC and C_{max} did not differ

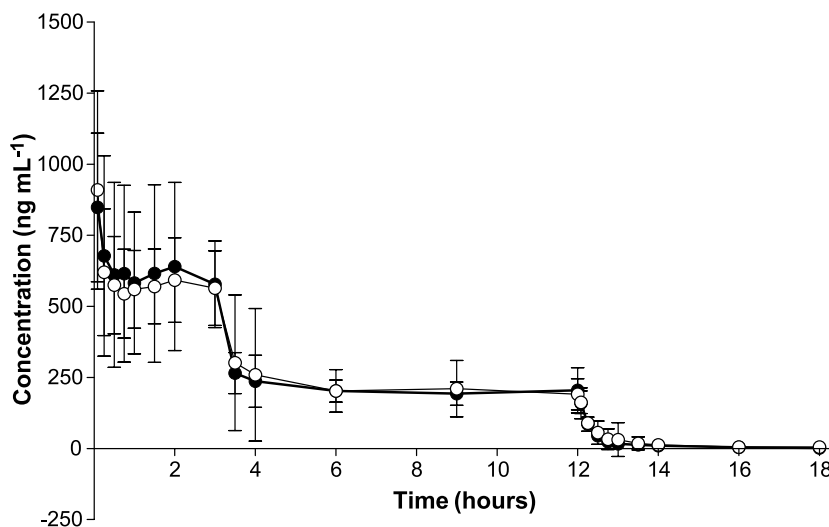


Fig. 2. Mean (\pm SD) plasma concentration–time curves ($n = 13$) of atosiban when administered alone (○) or in combination with an oral dose of 100 mg labetalol twice daily (●).

Table 1. Pharmacokinetic parameters of atosiban (Treatment A) and labetalol (Treatment B) administered alone or in combination (Treatment C) to healthy female volunteers ($n = 13$). The AUC, C_{max} and C_{min} are presented as geometric means and CV%, whereas t_{max} is presented as the median and range. C_{max1} and t_{max1} refer to the dose of labetalol given simultaneous with the start of atosiban infusion, whereas C_{max2} and t_{max2} refer to the dose of labetalol given 12 hours later.

	Atosiban (A)	Labetalol/Atosiban (C)	Ratio C/A (%)	90% CI
Atosiban				
AUC (h ng mL ⁻¹)	3581 (24%)	3852 (27%)	105% ^a	98%, 111% ^a
C_{max} (ng mL ⁻¹)	963 (23%)	867 (36%)	– ^b	– ^b
	Labetalol (B)	Labetalol/Atosiban (C)	Ratio C/B (%)	90% CI
Labetalol				
AUC _{ss} (h ng mL ⁻¹)	571 (44%)	568 (40%)	99.5%	91%, 108%
C_{max1} (ng mL ⁻¹)	72.4 (54%)	46.5 (50%)	64%	49%, 83%
t_{max1} (h)	2.0 (0.5–4.0)	3.0 (1–4.0)	0.75 h ^c	0.0 h, 1.6 h ^c
C_{max2} (ng mL ⁻¹)	58.2 (67%)	67.1 (28%)	106.5%	94%, 139%
t_{max2} (h)	13 (12.5–24)	14 (12.5–16)	0.25 h ^c	–0.5 h, 0.75 h ^c
C_{min} (ng mL ⁻¹)	8.5 (82%)	9.0 (53%)	96.3%	86%, 113%

^a $n = 10$.

^b Not calculated.

^c Non-parametric evaluation.

relevantly between monotherapy and combination treatments, and all 90% CIs for ratios between treatments were well within limits (80%, 125%) (Table 2).

For one participant, the AUC for atosiban could not be calculated because the concentration–time profile in the elimination phase did not show a recognisable log-linear decrease. The exclusion of this participant did not affect the overall statistical significance of the tests. The CIs for t_{max} included zero, and thus, no statistically significant difference was seen for this parameter (Table 2).

In Study 1, 11 of 14 patients receiving the atosiban infusion alone experienced 23 adverse events, of which 11

were considered to be drug related. Of the drug-related adverse events, headache and nausea of mild-to-moderate intensity were reported most often. During treatment with labetalol monotherapy, 9 of 14 participants reported 31 adverse events. Twenty-nine of these events were considered to be drug related. Mild-to-moderate headache and fatigue were reported most frequently. One participant experienced headache of severe intensity, and requested to be withdrawn from the study due to pharyngitis (not drug related). With the combination treatment, 9 of 13 participants reported 12 adverse events, of which 11 were considered to be drug related. The two adverse events reported

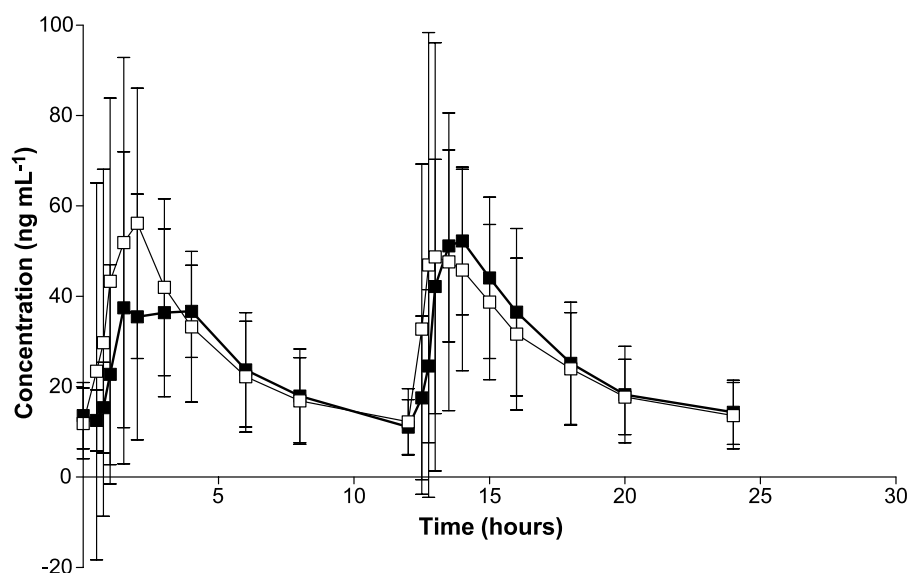


Fig. 3. Mean (\pm SD) plasma concentration–time curves ($n = 13$) of an oral dose of 100 mg labetalol twice daily when administered alone (\square) or in combination with an intravenous infusion of 114.75 mg atosiban/12 hours (\blacksquare).

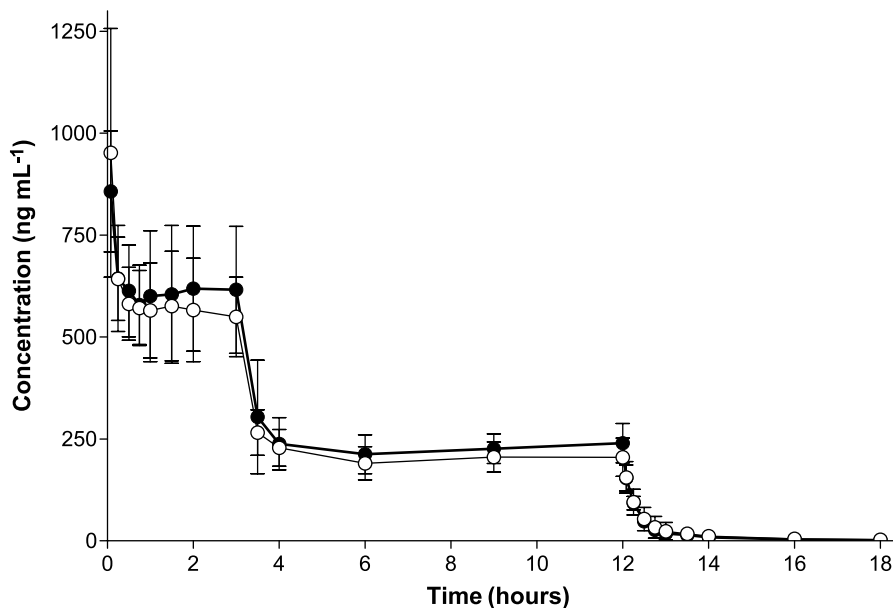


Fig. 4. Mean (\pm SD) plasma concentration–time curves ($n = 17$) of atosiban when administered alone (\circ) or in combination with a single intramuscular injection of 12 mg betamethasone (\bullet).

most often were mild headache and mild-to-moderate nausea. One participant developed a syncope lasting for 2 minutes, 2 hours after drug administration, although the reason for this was not apparent. This adverse event was considered to be of severe intensity.

After the labetalol combination treatment, changes in vital signs (e.g. decreases in blood pressure and increase in pulse) were comparable to those with atosiban alone. Labetalol given for four days had no effect upon blood

pressure or heart rate. In the post-study examination, 7 of 14 participants presented abnormal laboratory parameters. Most of these were due to low haemoglobin and none were considered serious.

The combination of atosiban with betamethasone resulted in a similar tolerability profile to the administration of each substance alone. Following atosiban monotherapy, 18 adverse events were reported in 10 participants, of which 14 adverse events in 8 participants were considered to be

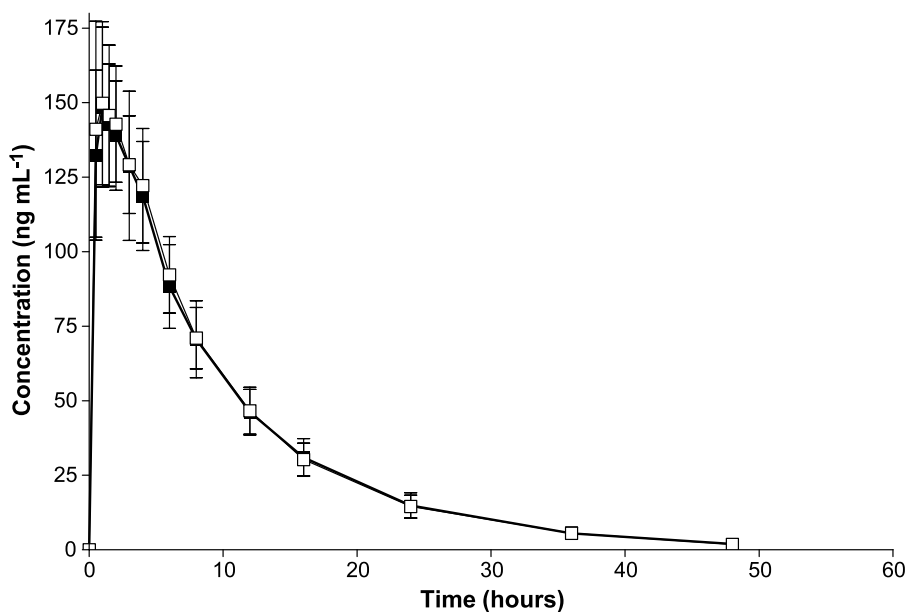


Fig. 5. Mean (\pm SD) plasma concentration–time curves ($n = 18$) of betamethasone when administered alone (\square) or in combination with an intravenous infusion of 114.75 mg atosiban/12 hours (\blacksquare).

Table 2. Pharmacokinetic parameters of atosiban (Treatment A) and betamethasone (Treatment B) administered alone or in combination (Treatment C) to healthy female volunteers ($n = 18$). The AUC and the C_{\max} are presented as geometric means and CV%, whereas t_{\max} is presented as median and range.

	Atosiban (A)	Betamethasone/Atosiban (C)	Ratio C/A (%)	90% CI
Atosiban				
AUC (h ng mL ⁻¹)	3787 (14%)	4059 (18%)	107.6%	103%, 112%
C_{\max} (ng mL ⁻¹)	925 (28%)	856 (20%)	92.7%	84%, 102%
t_{\max} (min)	5 (5–30)	5 (5–120)	0.0 h ^a	0.0 h, 0.5 h ^a
	Betamethasone (B)	Betamethasone/Atosiban (C)	Ratio C/B (%)	90% CI
Betamethasone				
AUC (h ng mL ⁻¹)	1636 (14%)	1633 (14%)	99.8%	97%, 103%
C_{\max} (ng mL ⁻¹)	157 (13%)	155 (15%)	98.6%	94%, 104%
t_{\max} (h)	1 (0.5–4)	1 (0.5–3)	-0.05 h ^a	-0.25 h, 0.0 h ^a

^a Non-parametric evaluation.

drug related. Of the drug-related adverse events, headache was reported most often. After the injection of betamethasone alone, nine adverse events were reported in six participants, of which seven events in five participants were considered to be drug related. Of the drug-related adverse events, headache was reported most frequently. After betamethasone monotherapy, 10 adverse events were reported in five participants and 7 events in three participants were considered to be drug-related. The most commonly reported drug-related adverse events were mild headache and skin disorders, such as erythematous rash. Injection site reactions were rare, irrespective of the treatment.

Overall, in Study 2, all the three treatments were well tolerated with regard to laboratory parameters and vital signs. Blood pressure dropped slightly after the start of treatment, however, the course was similar for all three groups. In contrast, pulse increased after the start of treatment (mean pulse [SD], $n = 8$: 66.6 [10.4] for pre-dose, 75 [7.4] for atosiban, 80.3 [10.2] for betamethasone and 81.9 [10.5] for the combination therapy). This was most pronounced for the combination therapy.

DISCUSSION

The results of the first trial indicate that the co-administration of atosiban and labetalol does not influence the bioavailability of atosiban, as assessed by AUC. Similarly, combination therapy had no relevant influence on labetalol bioavailability, as the AUC_{ss} was not affected. However, an interaction-induced effect was observed for the rate of bioavailability, as the C_{\max} for labetalol was lowered by 36% and was achieved 45 minutes later than with labetalol monotherapy.

The major indication for labetalol administered orally to pregnant women with threatening preterm delivery is for hypertension and mild-to-moderate pre-eclampsia.⁸ The reduction of C_{\max} and prolongation of t_{\max} in the observed range was not considered clinically relevant, as labetalol and other antihypertensives are usually administered for

the duration of the pregnancy, and the AUC_{ss} (hence, C_{ss}) did not change. Furthermore, only the dose of labetalol given simultaneously with the start of the atosiban infusion was affected and no interaction was seen when labetalol was given immediately after the discontinuation of atosiban. The observed effect was considered only of short duration, and this further supports the clinical irrelevance of this interaction. In severe cases of pre-eclampsia when an immediate treatment response is required, labetalol is administered intravenously, hence, no drug–drug interaction would be expected as the above interaction was considered to be due to oral absorption.

The administration of atosiban and labetalol in combination resulted in a similar tolerability profile to that for each substance administered alone. Most adverse events were considered to be mild or moderate in severity, although 7 of 14 women presented abnormal laboratory findings in the post-study examination. Most of these (decrease in red blood cells) could be attributed to frequent blood sampling during the study course. Changes in vital signs, such as a fall in blood pressure and increase in pulse rate, were comparable to those after atosiban alone. Labetalol given for four days did not have any effect upon blood pressure or heart rate. This can be explained by the fact that antihypertensive drugs are much more effective in hypertensive than in normotensive participants. With regard to safety, the combination of atosiban and labetalol did not increase the frequency of adverse events and did not result in an increased pharmacodynamic effect upon vital signs.

Previous *in vitro* studies with atosiban and betamethasone clearly indicate that it was highly unlikely that a pharmacokinetic drug–drug interaction would occur *in vivo* (unpublished data).

The results of the second interaction study are very conclusive. Based on the CI inclusion rule for AUC and C_{\max} and an assessment of t_{\max} , it can be concluded that the co-administration of atosiban had no clinically relevant influence on the bioavailability of betamethasone. Similarly, the co-administration of betamethasone had no clinically relevant influence on the bioavailability of atosiban.

The pharmacokinetic data obtained in the present study are similar to those previously published for pregnant women with preterm uterine contractions.⁴

In Study 2, the frequency of adverse events was highest during atosiban monotherapy. However, the adverse events, with headache reported most often, were all of mild-to-moderate intensity and in agreement with observations from a previous clinical trial in this target patient population.²⁴ During betamethasone monotherapy and in combination with atosiban, adverse events were less frequent with mild-to-moderate headache reported most often. Overall, the co-administration of atosiban and betamethasone resulted in similar tolerability as the administration of each substance alone.

As a first-line tocolytic agent, the safety of atosiban has been well documented in several large and well-controlled trials.^{7,25,26} The results of this study demonstrate that atosiban can be safely prescribed with drugs used to treat common conditions during pregnancy.

In conclusion, the bioavailability of atosiban was not affected by concomitant treatment with labetalol, and the extent of bioavailability of labetalol was not changed during co-administration with atosiban in non-pregnant healthy female volunteers. The observed decrease in C_{max} and increase in t_{max} for labetalol during the atosiban infusion are probably of limited clinical relevance, as the AUC_{ss} and C_{min} were not changed. With betamethasone, there was no change in any of the pharmacokinetic parameters during co-administration. Thus, it can be concluded that there were no clinically relevant pharmacokinetic interactions between atosiban and betamethasone in non-pregnant healthy female volunteers.

In summary, the use of atosiban with the commercially prescribed medicines, labetalol and betamethasone, during pregnancy has revealed a lack of pharmacokinetic interactions or changes in tolerability, with no serious adverse events being noted. This may be beneficial for women with threatening preterm delivery.

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